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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/555,534	ENSOLI, BARBARA	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *124-126,169-178 and 192-198* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/8/08*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-128 and 142-198.

Continuation of Disposition of Claims: Claims rejected are 62,63,65,66,68,69,89-103,105-112,114,116,117,119,121-123,127,128,142-168 and 179-191.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08 May 2008 has been entered.

DETAILED ACTION

Claims 1-61, 64, 67, 70-88, 104, 113, 115, 118, 120 and 129-141 have been cancelled. Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119,121-128 and 142-198 are pending. Claims 169-178, 124-126 and 192-198 are withdrawn. Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168 and 179-191 are currently examined.

The objection to claims 62, 125 and 126 is **withdrawn** in response to Applicant's amendment.

Priority

Receipt is acknowledged of foreign priority document, Italy RM97A000743, submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Therefore, the foreign priority date is deemed to be the filing date of the Italian application RM97A000743 (01 December 1997).

Claim Rejections - 35 USC § 112 - New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168 and 179-191 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The phrase "wherein said composition is pharmaceutically acceptable for administration to a human" is not supported by the original disclosure or claim as filed. The specification of the instant application does not describe a HIV-1 Tat composition that is rid of the toxic HPLC solvents like acetonitrile and trifluoroacetic acid (TFA) and the neurotoxic serine protease inhibitor like phenylmethanesulphonylfluoride or phenylmethylsulphonyl fluoride (PMSF). The specification even cites the Chang (1997) reference and specifically states the inclusion of PMSF in the heparin affinity purification method. See page 25, line 5-7 and line 15. Therefore, the claims represent a departure from the specification and claims as originally filed.

Examiner has stated this fact as a reason for maintaining the prior art rejection over Chang in the Office Action (on top of page 3) mailed on 01 November 2006. Applicant failed to address this issue in the response while alleging that the Chang reference does not teach a pharmaceutical Tat composition acceptable for administration to humans. According to Applicant's contention and Dr. Barbara Ensoli's declaration filed on 13 December 2005 under 37 C.F.R. §1.132 (page 2, last sentence), the HIV-1 Tat protein prepared by the methods as disclosed in the instant application and in Chang *et al*. contains toxic organic solvents such as acetonitrile and trifluoroacetic acid. In conclusion, the disclosure of the application as filed does not support the limitation that the instantly claimed composition is "pharmaceutically acceptable for administration to a human."

Such limitation, as recited in the present claims, does not appear in the claims or specification, as filed, and introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. §112. Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the limitation indicated above. See MPEP §714.02, §2163.05-06 and §2173.05(i).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 128, 142-150, 152,153, 155-159, 161,162, 164-168, 179-183, 185, and 186 under 35 U.S.C. §102(b) as being anticipated by Chang *et al.* (11 October 1997) is **withdrawn** upon further consideration and in favor of the following new grounds of rejection under 35 U.S.C. §103.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 114, 119, 128,142-150, 152,153, 155-159, 161,162, 164-168, 179-183, 185, 186 and 189 under 35 U.S.C. §103(a) as obvious over Chang et al. in view of Heiman *et al.* (1998) is **withdrawn** in favor of a new rejection.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-95, 97, 101-103, 105-111,116, 117, 121,122, 128, 142-168, 179-187,190, and 191 under 35 U.S.C. §103(a)

as obvious over Chang *et al*. (11 October 1997) in view of Vogel *et al*. (1995) is **withdrawn** in favor of a new rejection.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 99, 106, 107, 128, 142-150, 152, 153, 155-159, 161,162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang *et al*. (11 October 1997) in view of Castignolles *et al*. (is **withdrawn** in favor of a new rejection.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94,100, 106, 107,128, 142-150, 152, 153, 155-159, 161,162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang *et al*. (11 October 1997) in view of Ramshaw *et al*. is **withdrawn** in favor of a new rejection.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 112, 128, 142-150, 152, 153, 155-159, 161,162, 164-168,179-183,185, 186, and 188 under 35 U.S.C. §103(a) as obvious over Chang et al. (11 October 1997) in view of Livingston *et al*. is **withdrawn** in favor of a new rejection.

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93-94, 106, 107, 123, 128, 142-150, 152, 153,155-159, 161, 162, 164-168, 179-183, 185 and 186 under 35 U.S.C. §103(a) as obvious over Chang et al. in view of Barry *et al*. is **withdrawn** in favor of a new rejection.

Response to Arguments

Applicant's response has condensed the traversal of the six prior art rejections into one general discussion rather than directing arguments to each specific rejection.

This renders unclear the relevance of each argument to each ground of rejection of record. Therefore, Applicants' arguments have been addressed to the extent that they read on each of the six rejections under 35 U.S.C. §103.

In response to applicant's disagreement with Examiner's summary of the two Magnani declarations filed on 01 May 2007 and 19 October 2007, respectively, Examiner respectfully points out that, however applicant rephrases the gist of the Magnani declarations, Dr. Magnani stated on the record that one skilled in the art as of 1 December 1997 could obtain a composition containing a biologically active Tat that is pharmaceutically acceptable for administration to a human, based on knowledge common in the art as of 1 December 1997 and using only routine experimentation (page 3 of the supplemental declaration, lines 4-7).

Applicant's arguments with respect to claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168 and 179-191 have been considered but are moot in view of the new grounds of rejection.

New Rejections

Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al*. (11 October 1997) in view of Sumner-Smith *et al*. (US 5,646,120, patented 8 July 1997) and as evidenced by Gu *et al*. (1994).

The instant claims read on a composition comprising an isolated Tat protein in combination with a pharmaceutically acceptable carrier or excipients, wherein said isolated Tat protein is biologically active and acceptable for administration to a human.

Chang *et al*. teach a composition comprising fully biologically active HIV Tat proteins, which are isolated by successive rounds of high-pressure liquid chromatography (HPLC) and ion-exchange chromatography (IEC), stored by lyophilization at -70^{o}C and resuspended in degassed buffer, PBS containing 0.1% BSA and 0.1 mM DTT to prevent oxidation and loss of biological activity before use (page 1424, left column, Tat protein and anti-Tat antibody).

Chang *et al*. does not expressly teach removing organic solvents such as acetonitrile and trifluoroacetic acid (TFA) at the end of the protein preparation to render the Tat protein acceptable for administration to a human. However, the lyophilization process disclosed by Chang *et al*. necessarily removes the acetonitrile, as evidenced by Gu *et al*., who discloses that ACN is removed by evaporation or freeze-drying (Abstract).

Gu *et al*. further discloses phase separation of acetonitrile-water mixture in protein purification, wherein the an effluent fraction containing 65% (vol.) acetonitrile/35% water/0.1% TFA is stored in a freezer at -17^{o}C for several hours or overnight, the bottom phase containing 65% water, which contains 99%+ of the total protein, and 35% acetonitrile remains unfrozen (page 258, right column, first two paragraphs) and this reduced volume of solvent can be easily lyophilized, which removes acetonitrile.

Sumner-Smith *et al.* discloses that a peptide purified by HPLC and IEC is typically then treated to exchange the cleavage acid (e.g. TFA) with a pharmaceutically acceptable acid, such as acetic acid, to provide a water soluble salt of the peptide (column 9, lines 47-62). For therapeutic use, proteins exhibiting pharmaceutical grade purity are combined with pharmaceutically acceptable carriers to generate compositions suitable for administration to patients (column 10, lines 19-34).

Chang *et al.* also discloses purification of HIV Tat protein by heparin affinity chromatography (page 1424, bottom of left column). Even though there is no suggestion to avoid the use of PMSF in Chang *et al.*, applicant has admitted on the record, as evidence by the two Magnani declarations (page 2 of the supplemental declaration filed on 19 October 2007), that it is common knowledge and routine experimentation in the art as of 1 December 1997 that a combination of purification steps should decrease levels of endotoxin in the resulting protein preparation and to avoid the use of PMSF in the process by purifying a protein at a pH or a temperature, e.g. near 0^{o}C, that inactivates proteases without harming the protein of interest.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV-1 Tat composition of Chang *et al.* so as to include a further step of treating the purified Tat protein with a pharmaceutically acceptable acid with a reasonable expectation of success because the prior art suggests that procedure to exchange the TFA for therapeutic use. The skilled artisan would have been motivated to do so to generate a Tat composition acceptable for administration to patients. There would have been a reasonable expectation of success

since one skilled in the art has been routinely removing the acetonitrile by lyophilization, as evidenced by Gu *et al*. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 114, 119, 127, 128, 142-153, 155-162, 164-168, 179-186 and 189 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al*. (11 October 1997) in view of Sumner-Smith *et al*. (US 5,646,120, patented 8 July 1997) and Heiman *et al*. (1998), and as evidenced by Gu *et al*. (1994).

The instant invention is further limited to an isolated HIV Tat protein fused to HIV Rev, Nef or Gag, or an immunogenic fragment thereof.

The relevance of Chang *et al*., Sumner-Smith *et al*. and Gu *et al*. is set forth above. These references do not disclose fusing HIV Tat to other HIV protein.

The review article by Heiman *et al*. describes numerous combinations of HIV proteins known in the art. They specifically disclose Gag at pages 3-5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine or fuse the HIV Tat protein of Chang *et al*. with the HIV Gag antigen of Heiman *et al*. so as to link the gag immune response with the Tat protein response with the expectation of at least an additive effect. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 62, 63, 65, 66, 68, 69, 89-97, 101-103, 105-111, 116, 117, 121, 122, 127, 128, 142-168, 179-187, 190, and 191 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al*. (11 October 1997) in view of Sumner-Smith *et al*. (US 5,646,120, patented 8 July 1997) and Vogel *et al*. (1995), and as evidenced by Gu *et al*. (1994).

The instant invention is further limited to a HIV-1 Tat protein fused to a cytokine, specifically, IL-12, and added an adjuvant such as alum.

The relevance of Chang *et al*., Sumner-Smith *et al*. and Gu *et al*. is set forth above. These references do not disclose fusing HIV Tat to a cytokine like IL-12 or adding an adjuvant such as alum.

Vogel *et al*. discloses that IL-2 modulates the immune System through the T cell pathway. See entire reference. Vogel *et al*. further discloses that alum is a well known and studied adjuvant. As the authors note in the introductory paragraph on page I, alum is the only adjuvant used in human vaccine licensed in the United States.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add this cytokine to the composition of Chang *et al*. so as to link the favorable immune response with the Tat protein with the expectation of favorably modulating the immune system. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to add a well known adjuvant, alum, to the composition of Chang *et al*. with the expectation of enhancing the immune reaction to Tat. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 99, 101-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al*. (11 October 1997) in view of Sumner-Smith *et al*. (US 5,646,120, patented 8 July 1997) and Castignolles *et al*. (1996), and as evidenced by Gu *et al*. (1994).

The instant invention is further limited to a HIV-1 Tat protein bound to a nanoparticle.

The relevance of Chang *et al*., Sumner-Smith *et al*. and Gu *et al*. is set forth above. These references do not disclose binding HIV-1 Tat protein to a particle.

Castignolles *et al*. suggests that nanoparticles have immunostimulating properties. See the abstract and the discussion section.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the nanoparticles of Castignolles *et al*. with the Tat protein of Chang *et al*. with the expectation of enhancing the immune response to the protein. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 100-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al*. (11 October 1997) in view of Sumner-Smith *et al*. (US

5,646,120, patented 8 July 1997) and Ramshaw et al. (1977), and as evidenced by Gu *et al.* (1994).

The instant invention is further limited to a HIV-1 Tat protein bound to an autologous erythrocyte.

The relevance of Chang *et al.*, Sumner-Smith *et al.* and Gu *et al.* is set forth above. These references do not disclose a HIV-1 Tat protein bound to an autologous erythrocyte.

Ramshaw *et al.* discloses that autologous erythrocytes (red blood cells) coupled to antigens can enhances an immune response of the antigen. See page 255.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to couple the HIV Tat protein of Chang *et al.* to autologous erythrocytes, as per the suggestion of Ramshaw *et al.*, to enhance the immune response of the HIV Tat protein antigen. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 112, 127, 128, 142-153, 155-162, 164-168, 179-186 and 188 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and Livingston *et al.* (August 1997), and as evidenced by Gu *et al.* (1994).

The instant invention is further limited to a HIV-1 Tat protein conjugated to a T-helper universal epitope of tetanus toxoid.

The relevance of Chang *et al.*, Sumner-Smith *et al.* and Gu *et al.* is set forth above. These references do not disclose conjugating the HIV-1 Tat protein to a T-helper universal epitope of tetanus toxoid.

Livingston *et al.* suggests that conjugating the T helper epitope of tetanus toxoid to hepatitis B virus surface antigen (HBsAg) enhances the immunogenicity of the HBsAg. See the entire reference. Note that the reference teaches, on the first page, second column, that the T helper epitope of tetanus toxoid is a universal HTL epitope which greatly potentiates the CTL responses elicited by a vaccine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the T cell helper epitope of tetanus toxin of Livingston *et al.* to the HIV Tat protein of Chang *et al.* One would be motivated to do this in order to enhance the CTL response of the HIV Tat protein. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 123, 127, 128, 142-153, 155-162, 164-168 and 179-186 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chang *et al.* (11 October 1997) in view of Sumner-Smith *et al.* (US 5,646,120, patented 8 July 1997) and Barry *et al.* (March 1997), and as evidenced by Gu *et al.* (1994).

The instant invention is further limited to a HIV-1 Tat protein combined with an inhibitor of viral replication.

The relevance of Chang *et al.*, Sumner-Smith *et al.* and Gu *et al.* is set forth above. These references do not disclose adding an inhibitor of viral replication to the HIV-1 Tat protein.

Barry *et al.* discloses various viral inhibitor compounds known in the art. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add an antiviral inhibitor, as suggested by Barry *et al.*, to the HIV Tat protein, as taught by Chen *et al.*, in a combination therapy for an additive effect of viral inhibition. One skilled in the art would be motivated to do so for the inhibition of a virus like HIV, which is known in the art to evolve into drug-resistant viral strains as a result of monotherapy. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
2 July 2008

/Bruce Campell/

Supervisory Patent Examiner, Art Unit 1648